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Radioiodine ablation of thyroid remnants in patients with differentiated thyroid carcinoma (DTC) following administration of rhTSH — a comparison with L-thyroxine withdrawal

Ablacja resztkowej tarczycy radiojodem u chorych na zróżnicowanego raka tarczycy (DTC) za pomocą rhTSH — porównanie ze stymulacją endogenną po odstawieniu L-tyroksyny

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Abstract

Introduction: A group of differentiated thyroid carcinoma (DTC) patients receiving post thyroidectomy rhTSH-aided radioiodine treatment (group I) was compared with patients treated with ^{131}I following endogenous stimulation of TSH (group II) after L-thyroxine withdrawal.
Materials and methods: Group I consisted of 66 patients of mean age 51.7 ± 16.2 years (58 females and 8 males). Group II included 76 patients of mean age 54.8 ± 14.7 years (67 females and 9 males). All patients underwent total thyroidectomy and central lymph node dissection and additionally lateral lymph node excision, if required. Prior to radioiodine treatment thyroid volume (VT) and 24-hour ^{131}I uptake were evaluated. TSH and Tg concentrations were measured prior to and after endogenous and exogenous stimulation of TSH. Whole-body post-therapeutic scintigraphy was evaluated. Basic statistics, W Shapiro-Wilk, Wilcoxon, and U Mann-Whitney tests were applied.
Results: Median values of VT and of 24-hr ^{131}I uptake in groups I and II were not significantly different. The differences between median values of serum TSH concentration after stimulation in groups I and II were statistically significant ($p < 0.05$), respective medians being 100.0 μU/mL (IQR = 107.3) and 78.8 μU/mL (IQR = 47.7). Median values of serum Tg concentrations in groups I and II following TSH stimulation prior to radioiodine treatment were 2.6 ng/ml (IQR = 8.4) and 4.9 ng/ml (IQR = 12.6), respectively, the difference not being statistically significant. Following rhTSH treatment no adverse effects were observed compared to LT4 withdrawal.
Conclusions: rhTSH may be safely used for ^{131}I thyroid remnant ablation in low-risk DTC patients.
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Key words: *differentiated thyroid carcinoma, radioiodine treatment, rhTSH*

Streszczenie

Wstęp: Grupę pacjentów ze zróżnicowanym rakiem tarczycy leczonych ^{131}I za pomocą stymulacji z zastosowaniem rhTSH (grupa I) porównano z pacjentami leczonymi po endogennej stymulacji TSH (grupa II).
Materiał i metody: Grupa I składała się z 66 chorych (śr. wieku 51,7 ± 16,2 lat, 58 kobiet, 8 mężczyzn). Grupa II składała się z 76 chorych (śr. wieku 54,8 ± 14,7 lat, 67 kobiet, 9 mężczyzn). Leczenie chirurgiczne polegało na całkowitym wycięciu tarczycy i operacji węzłów chłonnych przedziału centralnego, a w razie potrzeby także operacji węzłów szyjnych bocznych. Przed leczeniem ^{131}I oceniano objętość kikutów tarczycy (VT) w badaniu USG oraz 24-godzinny wychwyt ^{131}I nad szyją. Stężenie TSH i Tg oznaczano przed i po stymulacji endo- i egzogennej TSH. Oceniano również gromadzenie ^{131}I w scyntygrafii poterapeutycznej całego ciała. Analizę statystyczną przeprowadzono za pomocą statystyki opisowej, testu W Shapiro-Wilka, testu Wilcoxona i testu U Mann-Whitneya.
Wyniki: Mediany objętości tarczycy oraz mediany wychwytu ^{131}I w grupie I i II nie różniły się znamiennie statystycznie. Mediany stężeń TSH w surowicy po stymulacji w grupie I i II różniły się istotnie ($p < 0,05$) i wynosiły odpowiednio 100,0 μj./ml (IQR = 107,3) i 78,8 μj./ml (IQR = 47,7). Mediany stężeń Tg w surowicy po stymulacji w grupie I i II przed leczeniem ^{131}I wynosiły odpowiednio 2,6 ng/ml (IQR = 8,4) i 4,9 ng/ml (IQR = 12,6) i nie różniły się znamiennie statystycznie. Nie obserwowano działań niepożądanych po zastosowaniu rhTSH w porównaniu z leczeniem po odstawieniu L-tyroksyny.
Wnioski: rhTSH może być bezpiecznie stosowane do ablacji kikutów tarczycy radiojodem ^{131}I u pacjentów ze zróżnicowanym rakiem tarczycy z grupy niskiego ryzyka. **(Endokrynol Pol 2010; 61 (5): 474–479)**

Słowa kluczowe: *zróżnicowany rak tarczycy, leczenie radiojodem, rhTSH*

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Introduction

It is generally understood that proliferation of thyroid follicular cells, normal and transformed, is regulated by TSH. Therefore, patients diagnosed with differentiated thyroid carcinoma (DTC) who have undergone total thyroidectomy are treated with TSH-suppressing doses of L-thyroxine (LT4). The low serum TSH concentration required in the interim has to be elevated for adjuvant ^{131}I radioiodine thyroid remnant ablation and radioiodine therapy of disseminated disease. In order to achieve high serum TSH concentrations [1] LT4 has to be withdrawn, causing severe hypothyroidism with all its costs and comorbidities. Recently, recombinant human thyrotropin (rhTSH) was introduced in differentiated thyroid carcinoma treatment and follow-up as a safe and effective alternative to LT4 withdrawal. The first clinical applications of rhTSH, introduced in the US in 1998 and in Europe in 2001, were in diagnostics, to evaluate stimulated thyroglobulin (Tg) concentrations and ^{131}I whole-body scans (WBS). After publication of a multicentre, randomized, controlled study [2], the EMEA (European Medicine Agency) in 2005 and the FDA (Food and Drug Administration) in 2007 approved rhTSH-aided ablation of thyroid remnants with 100 mCi of ^{131}I in low-risk patients. This was later extended to intermediate-risk patients with lymph node metastases [3]. ^{131}I treatment aided by rhTSH has not yet been approved for metastatic patients; however, several observations confirming the safety and efficacy of this treatment in advanced DTC have already been published [4, 5]. Recombinant human TSH stimulation offers better quality of life. It is also a cost-effective method, the high cost of rhTSH being offset by shorter sick-leave in patients treated. Finally, application of this method leads to lower absorbed whole-body dose, due to higher renal clearance, enabling higher therapeutic activities to be applied. In 2009 all DTC patients of our Clinic of Endocrinology were treated for the first time with the aid of recombinant human TSH.

We present a comparison between two groups of patients with differentiated thyroid carcinoma treated with radioiodine ^{131}I in 2009 following exogenous stimulation of TSH (group I), and in 2008 following endogenous stimulation (group II).

Material and methods

Group I consisted of 66 patients (58 females and 8 males) of mean age 51.7 ± 16.2 years. Papillary thyroid cancer was diagnosed in 58 patients (87.9%) and follicular cancer in 8 patients (12.1%). Group II consisted of 76 patients (67 females and 9 males) of mean age 54.8 ± ± 14.7 years, with papillary thyroid cancer diagnosed in 60 patients (78.9%) and follicular cancer in 13 patients (17.1%). Other variants of thyroid cancer (among them, Hürthle cell carcinoma) were diagnosed in 3 patients (3.9%) from this group. All patients in both groups underwent total thyroidectomy with central lymph node resection. Enlarged lateral lymph nodes, as stated in preoperative physical or USG examination, were also resected. The surgically obtained specimens underwent histopathological and additional immunohistochemical examination to state the presence of Tg in the lateral lymph nodes. In rhTSH-stimulated group I, the presence of metastases in the central lymph nodes was stated in 13/66 (19.7%) patients and the presence of metastases in lateral lymph nodes in 3/66 (4.5%) patients. In group II of the patients treated with endogenous TSH stimulation, the presence of metastases in the central lymph nodes was stated in 9/76 (11.8%) patients and the presence of metastases in lateral lymph nodes in 2/76 (2.6%) patients. Prior to surgery, no distant metastases were stated in either group of patients.

LT4 treatment was commenced immediately after surgery to suppress TSH levels. For radioiodine treatment, in group I on LT4 therapy, patients were administered 0.9 mg i.m. of rhTSH (Thyrogen, Genzyme) on two consecutive days and received radioiodine 24 hours after the second injection, according to a procedure described elsewhere [6]. In group II, LT4 was withdrawn four weeks prior to ^{131}I treatment.

In all patients prior to radioiodine treatment, thyroid volume (VT) was evaluated by sonography and 24-hr ^{131}I (0.1 mCi; 4 MBq) uptake over the neck was measured. Oral administration of 100 mCi (3700 MBq) was performed immediately after the neck scan was completed. Six days after ^{131}I administration post-therapeutic whole-body scintigraphy (WBS) was evaluated by a dual-head computed gamma camera equipped with high energy collimators (Siemens).

TSH (ECL, Roche) and Tg (ECL, Roche) concentrations were measured prior to and after exogenous stimulation of TSH, according to the general scheme of rhTSH trials [6]. In group II, TSH and Tg were measured prior to ^{131}I administration. The presence of anti-Tg antibodies was evaluated (ECL, Roche).

Basic statistics, W Shapiro-Wilk, Wilcoxon, U Mann-Whitney, ANOVA Friedman, and chi^2 tests were applied.

Results

No significant differences with respect to VT and 24-hr ^{131}I uptake were found between patients in group I (rhTSH stimulation) and those in group II (LT4 withdrawal), nor was the age at which DTC was diagnosed different in either group (Table I). In both groups of patients pooled

Table I. *Clinical characteristics of the studied patient groups*
Tabela I. *Charakterystyka kliniczna badanych grup pacjentów*

Group of patients	N	Age at diagnosis (yrs) × ± SD	Thyroid volume (VT) [mL]	^{131}I uptake (%)
Group I rhTSH	66	51.7 ± 16.2	0.5 ± 1.1	5.5 ± 3.1
Group II LT4withdrawal	76	54.8 ± 14.8	0.8 ± 1.1	8.0 ± 5.4
p (t-test)		> 0.05	> 0.05	> 0.05

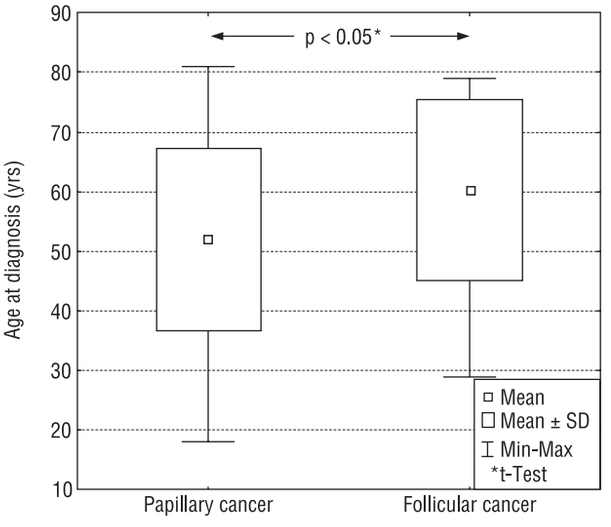

Figure 1. *Mean patient age at DTC histopathology diagnosis*
Rycina 1. *Średni wiek zachorowania pacjentów na DTC w zależności od rozpoznania histopatologicznego*

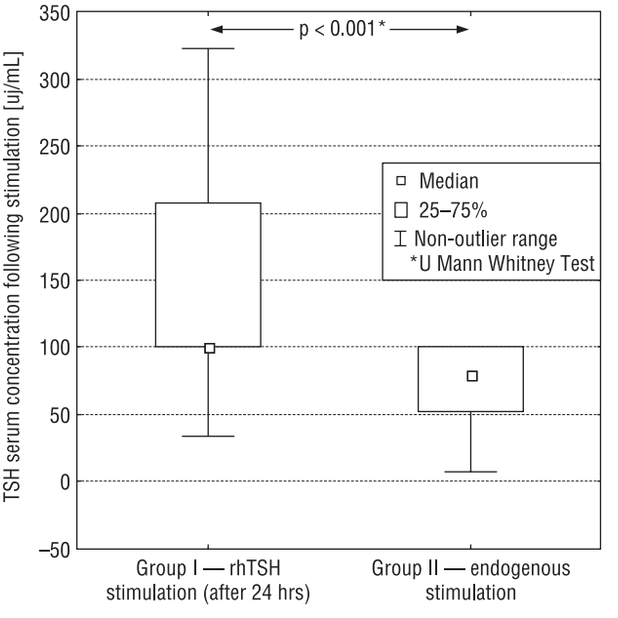

Figure 2. *TSH serum concentration after endogenous and rhTSH stimulation in the studied groups of patients*
Rycina 2. *Stężenie TSH w surowicy po stymulacji endogennej i rhTSH w badanych grupach pacjentów*

together (n = 142) the age interval at which differentiated thyroid carcinoma occurred most frequently was between 40 and 70 years of age, concerning about 60% of these patients. The mean age at which papillary or follicular cancer was diagnosed in our patients was significantly different: 52.0 ± 15.2 and 60.0 ± 16.1 years, respectively ($p < 0.05$) (Fig. 1).

Thyroid cancer staging was performed in all patients of each group according to AJCC/UICC criteria [7]. All patients below the age of 45 years in group I (n = 19) and group II (n = 18) were qualified as stage I. Patients over 45 years of age in group I (n = 38) were, in most cases (n = 23, 60.5%), also assigned stage I. In 3 patients (7.9%) stage II, and in 9 patients (23.7%) stage III was assigned, while the remaining 3 patients (7.9 %) were classified as stage IV. In 9 patients, DTC staging was not possible as the tumour size could not be determined (pTx). Patients over 45 years of age in group II (n = 51) were, in most cases (n = 33, 64.7%), assigned stage I. In 7 patients (13.7%) stage II, and in 9 patients (17.6%) stage III was assigned, while the remaining 2 patients (3.9%) were classified as stage IV. In 7 patients, DTC staging was not possible as the tumour size could not be determined (pTx). No difference in DTC staging was stated between the studied groups of patients, as based on contingency analysis (χ^2 test), $p > 0.05$.

After LT4 withdrawal or 24 hours after rhTSH injection, increased levels of TSH were observed. The differences between median values of TSH concentration prior to and after stimulation in group I and group II were statistically significant ($p < 0.001$), as expected. Immediately before rhTSH injection, serum TSH concentration was significantly higher in the hypothyroid group II 78.8 μU/mL (IQR = 47.7), as compared to group I 0.1 μU/mL (IQR = 0.9) ($p < 0.001$). After stimulation, the differences between median values of TSH concentrations in group I: 100.0 μU/mL (IQR = 107.3) and group II: 78.8 μU/mL (IQR = 47.7) were statistically significant ($p < 0.001$) (Fig. 2).

In group I of the patients which underwent rhTSH-aided ^{131}I treatment, a gradual increase in serum Tg concentration was observed, commencing with a median

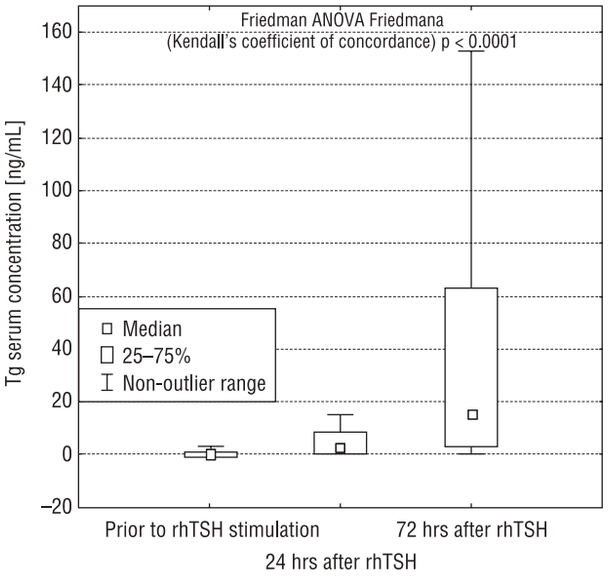

Figure 3. *Increase of Tg serum concentration after rhTSH stimulation over 72 hrs observation time in group II patients*

Rycina 3. *Wzrost stężenia Tg w surowicy pacjentów grupy II, po stymulacji rhTSH w czasie 72 godzin obserwacji*

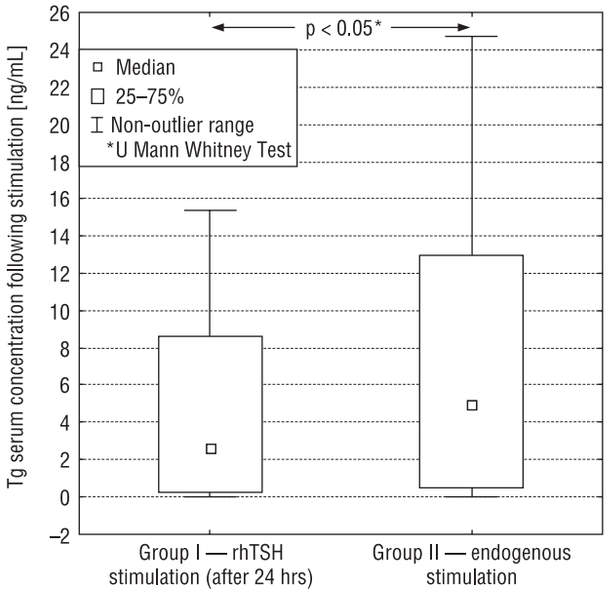

Figure 4. *Tg serum concentration 24 hrs after rhTSH stimulation and after endogenous TSH stimulation in the studied groups of patients*

Rycina 4. *Wzrost stężenia Tg w surowicy 24 godziny po stymulacji rhTSH i po stymulacji endogennej TSH w badanych grupach pacjentów*

value of 0.1 ng/mL (IQR = 1.0) up to median values of 2.6 ng/mL (IQR = 8.4) and 15.2 ng/mL (IQR = 60.2) 24 hrs and 72 hrs after rhTSH administration, respectively. All differences in these median values were statistically significant ($p < 0.0001$) (Fig. 3).

The median value of serum Tg concentrations in group I 24 hours after the last rhTSH administration (2.6 ng/mL, IQR = 8.4) was found to be lower than the median value of Tg concentration following LT4 withdrawal observed in group II (4.9 ng/mL, IQR = 12.6), the difference not being statistically significant ($p > 0.05$) (Fig. 4).

However, the median value of Tg concentrations in group I (15.2 ng/mL, IQR = 60.2) 72 hours after the last rhTSH administration was found to be significantly higher than the value (4.9 ng/mL; IQR = 12.6) observed in group II following LT4 withdrawal ($p < 0.001$) (Fig. 5).

The median levels of anti-Tg antibodies were 25.7 IU/mL (IQR = 126.4) and 17.9 IU/mL (IQR = 73.9) in groups I and group II, respectively, the difference not being statistically significant ($p > 0.05$).

On evaluation of post-therapeutic WBS, accumulation of tracer in thyroid remnants, was found in 98.5% and 98.7% of patient in groups I and II, respectively. The quality of post-therapeutic WBS after rhTSH-aided ^{131}I treatment was comparable to that of WBS following endogenous stimulation (Fig. 6).

In group I following rhTSH stimulated radioiodine therapy, further diagnostics was required in 11 patients (16.7%), in whom tracer accumulation was present in the lungs (2 patients), mediastinum (3 patients), and outside thyroid bed in the neck (6 patients). In none of the patients distant metastases were observed, based on CT and MRI scans. Since Tg concentration below 1 ng/ml was observed in all of these patients, non-specific accumulation of ^{131}I in the lungs was assumed. Tracer accumulation in the mediastinum most probably corresponded with ^{131}I uptake in the thymus remnants. Lymph node metastases were identified in 6 patients of group I, as verified by neck USG and FNAB. Thus, finally, in 6 cases the patients were rediagnosed with lymph node metastases. In group II, following endogenous TSH stimulation after LT4 withdrawal, 4 patients (5.3%) required verification due to ^{131}I uptake in the lungs (2 patients), mediastinum (1 patient), and neck (1 patient). Distant lung metastases were found in one patient, who demonstrated high serum Tg concentration (508.8 ng/ml). In 1 patient of group II, lymph node metastases were identified.

No correlations between volume of thyroid remnants and serum Tg concentration nor between ^{131}I uptake in the thyroid bed and Tg concentration prior to rhTSH stimulation were found.

In patients of group II, compared to patients of group I, signs and symptoms of hypothyroidism were observed. Following rhTSH treatment no adverse effects were noted.

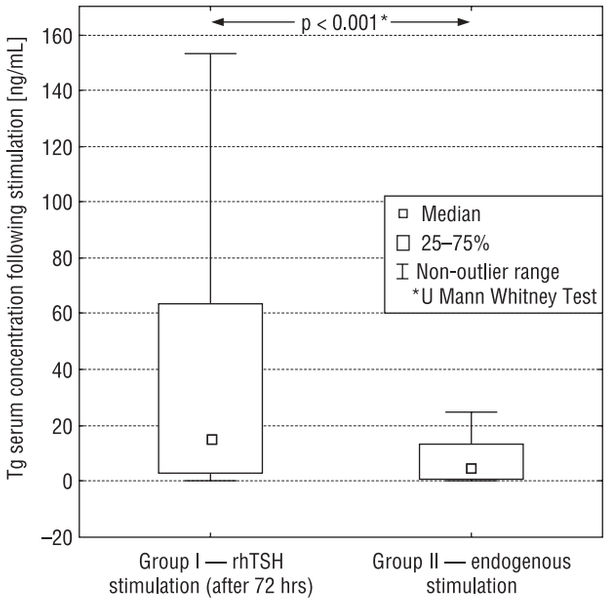

Figure 5. *Tg serum concentration 72 hrs after rhTSH stimulation and after endogenous TSH stimulation in the studied groups of patients*

Rycina 5. *Wzrost stężenia Tg w surowicy 72 godziny po stymulacji rhTSH i po stymulacji endogennej TSH w badanych grupach pacjentów*

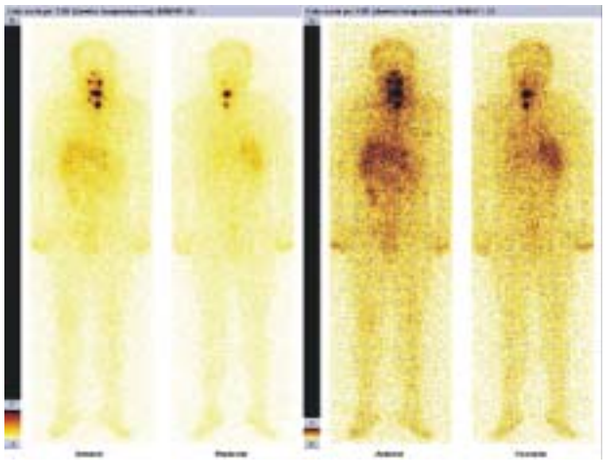

Figure 6. *Post-therapeutic WBS after rhTSH-aided ^{131}I treatment. Tracer uptake in neck lymph nodes outside the thyroid bed*

Rycina 6. *WBS poterapeutyczna po leczeniu ^{131}I wspomaganym stymulacją rhTSH. Gromadzenia znacznika w węzłach chłonnych szyi poza lożą tarczycy*

Discussion

Treatment of differentiated thyroid carcinoma (DTC) consists of total thyroidectomy followed by radioiodine ^{131}I thyroid remnant ablation and TSH suppression with LT4 [8, 9]. The rationale for ^{131}I ablation is to destroy any normal thyroid tissue which produces thyroglobulin, and to eliminate any microscopic foci of DTC. This procedure increases the specificity and sensitivity of Tg follow-up. In order to successfully apply ^{131}I treatment the TSH level must be elevated to above 30 μU/mL [1, 8], which can be achieved either by LT4 withdrawal or by application of recombinant human TSH. However, LT4 withdrawal induces clinically overt hypothyroidism with all its consequences [10]. Therefore, as soon as rhTSH-aided ^{131}I therapy became available in 2009, all DTC patients of our clinic were treated and diagnosed under continued LT4 treatment.

In this work, we compared a group of patients with differentiated thyroid carcinoma treated with ^{131}I in 2009, where radioiodine therapy following rhTSH stimulation could be applied with a group of patients treated in 2008 following endogenous stimulation. Our comparison is between groups similar with respect to age and quality of surgery, as indicated by no significant differences in VT and 24-hr ^{131}I uptake in patients of either group. Nor was a difference in DTC staging stated between the studied groups of patients.

The mean age of all our patients at diagnosis was about 10 years greater than that of the patients analyzed by Elisei et al. [11] and close to the value listed in the SEER base [12]. Additionally, the female to male ratio was different (7:1 in our group of patients versus 3:1), probably due to significant differences in the numbers of patients analyzed [11]. Dividing our patients according to histopathology results, those with follicular cancer were found to be about 10 years older than patients with papillary cancer, the difference being statistically significant and in agreement with general epidemiological data [13]. The frequency of papillary and follicular cancer was similar to that found in the published data (88% *v.* 12%) [11].

Some 60 % of our patients were diagnosed with thyroid cancer at the age of 40–70 years, in agreement with the age interval at which DTC occurred most frequently according to the SEER register [12].

Some 65% of our patients were qualified as stage I according to AJCC/UICC criteria [7], which agrees with the respective statistics of Elisei et al. [11] based on a large group of 4187 patients analysed at one Italian centre. However, our estimate of 3.5% (5/142) of patients qualified as stage IV does not agree with their estimates (10% of stage IV patients).

Recombinant human TSH stimulates the production of thyroglobulin and increases ^{131}I uptake in thyroid cancer patients remaining on LT4 suppression of TSH. Since the efficacy of rhTSH is comparable with LT4 withdrawal, it is now used in clinical practice for thyroid remnant ablation [2] and for follow-up of DTC patients [14].

Immediately before rhTSH injection, serum TSH concentration was significantly higher in hypothyroid group II as compared to group I. A significant increase in serum TSH concentration in group I was observed 24 hrs after the second rhTSH injection, indicating the efficacy of stimulation.

Similar behaviour was observed with respect to Tg concentration. After 24 hrs and after 72 hrs we observed a statistically significant increase of Tg concentration compared with the initial value prior to rhTSH administration.

After 24 hrs post administration of the last dose of rhTSH we found Tg concentration to be lower than that in group II of patients after withdrawal of LT4 four weeks earlier; however, the difference was not statistically significant.

After 72 hrs post administration of the last dose of rhTSH we found Tg concentration to be significantly higher than that in group II of patients who were investigated after withdrawal of LT4 but prior to ^{131}I administration. This observation could be explained by the effect of ^{131}I administration 24 hrs after the last dose of rhTSH in patients of group I and the Tg release from damaged thyroid cells which occurred only in those patients.

For thyroid remnant ablation in our patients we used 100 mCi (3.7 GBq) ^{131}I therapeutic activity since it was documented as being associated with a high rate of successful ablation in hypothyroid patients [15]. Also, Pacini et al. [2] demonstrated in a randomized, controlled study that standard activity of 100 mCi (3.7 MBq) is sufficient to ablate thyroid remnants in almost all patients while using rhTSH stimulation.

Thyroid remnant ^{131}I uptake on post-therapeutic WBS was seen in virtually all our patients of both groups, as found by Pacini et al. [2]. In our study ^{131}I uptake outside the thyroid bed on post-therapeutic WBS was observed more frequently in the rhTSH stimulated group (16.7% *v.* 5.3%) due to 6 patients in whom lymph node metastases were diagnosed concomitantly with ^{131}I treatment. Ladenson [16] suggests possible greater sensitivity of WBS and a higher level of Tg stimulation after withdrawal of LT4, but in his work diagnostic WBS and stimulated Tg were evaluated in post-ablative patients. We consider late diagnosis of lymph node metastases in some patients as the cause of the observed ^{131}I lymph node uptake.

We have demonstrated the safety of rhTSH aided ^{131}I primary therapy in DTC as no significant side effects were reported in group I after the administration of rhTSH, which is in agreement with the data from Barbaro et al. [17].

However, the efficacy of thyroid remnant ablation following LT4 withdrawal and rhTSH-aided treatment could not yet be evaluated and compared as in the patients from group I diagnostic WBS performed a year after thyroid ablation is necessary for this purpose. At present, only patients of group II treated with LT4 withdrawal have completed this step.

Conclusions

rhTSH may be safely used for ^{131}I thyroid remnant ablation in low-risk DTC patients.

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